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Periprosthetic infection risks and predictive value of HbA1c/albumin ratio for total joint arthroplasty in patients with diabetes mellitus

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Abstract. – OBJECTIVE: There are no gold standard markers to estimate the risk of developing periprosthetic infections in diabetes mellitus. Our aim is to compare the risks of periprosthetic infection in patients undergoing total joint arthroplasty with diabetes mellitus and to investigate the predictive significance of the HbA1c/albumin ratio.

PATIENTS AND METHODS: Between January 2012 and January 2020, 690 patients who underwent total joint arthroplasty were analysed. 264 diabetic patients were included in the study. 104 of them had periprosthetic infection. 8 risk factors (Hba1c/albumin, HbA1c, albumin, age, BMI, ASA, hospital stay, operation time) were analysed.

RESULTS: The rate of HbA1c/albumin was 14.6 times higher than the patients with ≤2.37 cut-off value. (Hba1c/albumin ratio (odds ratio (OR) = 14.6, 95% CI: 3.18-67.1, *p*: 0.01). HbA1c (OR = 2.6, 95% CI: 1.529-4.754, *p*: 0.001), BMI (OR = 1.6, 95% CI: 1.168-2.199, *p*<0.003), DM (OR = 0.365, 95% CI: 0.135-0.987, *p*: 0.04) and glucose (OR = 1.016, 95% CI: 1.004-1.029, *p*: 0.011) were risk factures for periprosthetic infection. Albumin (OR = 0.503, 95% CI: 0.109-2.314, *p*: 0.378) did not pose a significant risk for periprosthetic infection.

CONCLUSIONS: According to our findings, the HbA1c/albumin ratio has a more prognostic capacity than other risks in determining the risk of periprosthetic infection for total joint arthroplasty. HbA1c/albumin ratio is a cheap and easy-to-apply marker. Patients with an HbA1c/albumin cut-off ratio above 2.37 mg/dl in total joint arthroplasty should be followed more closely for the risk of periprosthetic infection.

Key Words:
HbA1c/albumin ratio, Periprosthetic infection, Risk factors, Total joint arthroplasty, Diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a common chronic disease that affects the quality of life of millions of people around the world. As a result of diabetes mellitus disease, they have pathological conditions that require more surgical intervention than normal healthy people[1]. In the literature, there are studies[1,2] showing that the risk of surgical complications and the length of hospital stay after surgery increase in patients with diabetes mellitus. Surgical intervention disrupts glucose blood regulation and causes hyperglycemia in the postoperative period[1,2].

Total joint arthroplasty (TJA) is an effective surgical procedure applied in patients with advanced gonarthrosis and coxarthrosis. Periprosthetic infection (PPI) is a difficult and common complication to treat in total joint arthroplasty[3]. Although measures such as antibiotic prophylaxis and new surgical techniques have increased recently, the number of infections is increasing with increasing surgery rates[4].

Albumin is a negative phase reactant that decreases during inflammation. An increased risk of infection at low albumin values has been shown in the literature[5]. Patients with diabetes with insufficient glycemic control have an increased risk rate for periprosthetic infection (PPI) and other systemic pathologies after TJA[6]. Should keep HgbA1c levels below 7% in patients with diabetes mellitus (normally between 4% and 7 %)[7]. Hemoglobin A1c (HgbA1c) is a serological marker showing an average systemic glucose concentration in the past 1 to 3 months[2,7]. An easy-to-apply and without additional costs scoring system may be needed to determine the PPI development risk rate. To the best of our knowledge, there is no study in the literature investigating the relationship of the HbA1c/albumin marker to PPI risk in patients with DM. Our goal is to investigate the risks of periprosthetic infection in TJA patients with DM, and to compare with the HbA1c/albumin ratio, and to investigate the predictive significance of the HbA1c/albumin ratio.

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Patients and Methods

We retrospectively analyzed 690 osteoarthritis patients who underwent total joint arthroplasty (TJA) between January 2012 and January 2020. We had 264 patients with diabetes mellitus. There were 40 patients in-group 1 (patients who developed infection after TJA with diabetes mellitus) and 224 patients in-group 2 (patients who did not develop infection after TJA with diabetes mellitus).

Eight risk factors (Hba1c/albumin, HbA1c, albumin, age, BMI, ASA, hospital stay, operation time) were analysed. The inclusion criteria were the absence of infection history in the joint and primary joint arthroplasty. Patients with incomplete patient data, secondary osteoarthritis, and that for any reason (trauma, cancer, and infection) previously had a history of surgical treatment in the joint were excluded.

All patients were routinely evaluated preoperatively. Anamnesis and clinical examination data were reviewed. Routine blood tests are performed before and after surgery, and urine and nasal cultures are taken. Total knee arthroplasty (TKA) was performed using standard medial parapatellar approach with using a tourniquet. Total hip arthroplasty (THA) was performed using either a direct lateral (modified Hardinge) or direct posterior (Kocher-langenbeck) approach. Antibiotic prophylaxis with 1 g of cefazolin every 8 hours was continued up to 48 hours after surgery. Clindamycin was given if the patient had a history of allergy to penicillin. One day after the operation, the drain was removed, muscle exercises were started and the patient was mobilized. All patients without any early complications were included in the physical therapy program at the 4th week after the operation. Clinical and radiographic follow-up was performed routinely in all patients at 2nd, 4th, 8th and 12th weeks after surgery. Clinical and radiographic follow-ups were continued in cases such as infection, limitation of ROM and continued pain.

The presence of PPI is defined according to the criteria of the international consensus[8]. A certain PPI is present when: (1) A sinus tract associated with a prosthesis, or (2) a bacterial growth in 2 or more fluid or tissue cultures from an infected prosthetic joint, or (3) if there are 3 of the following 5 criteria: (1) increased serum ESR and serum CRP; (2) increased synovial white blood cell count, or ++ change in the leukocyte esterase test strip; (3) increased synovial polymorph nuclear percentage; (4) positive histological analysis of periprosthetic tissue; and (5) a single positive culture.

The study was approved by the Ethics Review Committee of our faculty (188/04.06.2020). Written informed consent was obtained from all participants. All data were obtained without a personal identification document and made in accordance with the Declaration of Helsinki regulation.

Statistical Analysis

SPSS 23.0 statistical software (IBM Corp., Armonk, NY, USA) was used to analyse the measured data. Numerical data obtained in the study are shown as mean ± SD, (min-max), categorical data as frequency and percentage values. Chi-square test and Student's *t*-test were used to compare categorical data. Univariate Binary Logistic regression analysis was used to determine the effects of potential prognostic factors on infection. The diagnostic separation of HbA1c/albumin in infection was examined by area under the curve (AUC) (Figure 1) and ROC curve analysis[9].

In statistical analysis, $p<0.05$ was considered statistically significant with 95% confidence interval and 5% margin of error.

Results

One hundred sixty-eight (24.3%) of 690 patients were male and 522 (75.7%) were female. We had 104 (15.07%) patients with periprosthetic

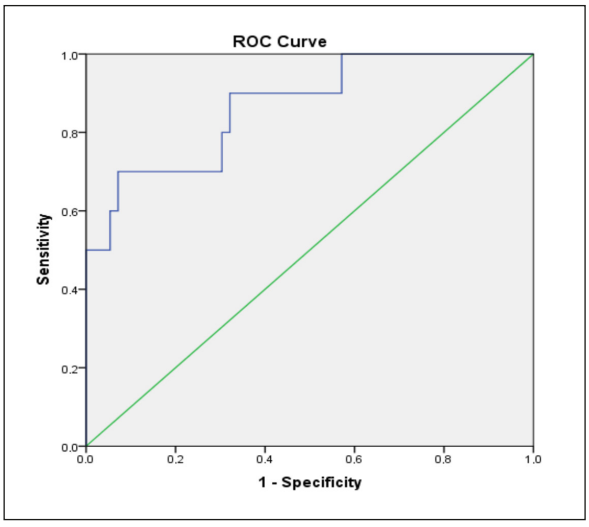

Figure 1. Area Under the Curve.

Table I. Patents data.

	Total knee arthroplasty	Total hip arthroplasty
Gender	358 f/66 m	164 f/102 m
Age	64.7 ± 5.2 years	57.9 ± 12 years
BMI	30.4 ± 3.7	28.1 ± 3.6
DM	180	84
Follow-up time	57.61 ± 21.4	59.4 ± 19.3
Operation time	173.06 ± 24.9 minutes	134.4 ± 15.5 minutes
Hospital stay	4.2 ± 1.7 days	5.5 ± 3.9 days
Periprosthetic infection	72	32

infections. Our mean follow-up was 58.3 ± 1.1 months. The distribution of patients according to TKA and THA are given in Table I.

Evaluation of Univariate Risk Factors for PPI in Patients With DM

We had 264 patients with diabetes mellitus and 40 (15.15%) of them had PPI infection.12 *Staphylococcus epidermidis*, 20 Methicillin Resistant *Staphylococcus Aureus* and 8 Methicillin Sensitive *Staphylococcus Aureus* bacterial strains grew in wound cultures. (OR = 2.64, 95% CI: 1.25-5.55, *p*: 0.017)

HbA1c/albumin (*p*:0.00), HbA1c (*p*:0.02), glucose (*p*:0.05), operation time (*p*: 0.033) and BMI (*p*:0.01) also showed a significant difference between group 1 and group 2 according to the Student's *t*-test. There was no significant difference between group 1 and group 2 according to Student's *t*-test in ASA (*p*: 0.036), age (*p*: 0.884), albumin (*p*: 0.502) and hospital stay (*p*: 0.535) (Table II).

Cut Off Values for Periprosthetic Infection in Patients with Diabetes Mellitus

The cut-off value for the ratio of HbA1c/albumin to infection was 2.37. Thirty-two patients in group 1 and 184 patients in-group 2 were above the 2.37 cut-off value (*p*: 0.01). The AUC corresponding to HbA1c/albumin has proven to be the best indicator for PPI. Sensitivity and specificity were 0.90 and 0.62, respectively. The AUC was 0.868 (*p*:0.00) with moderate accuracy. We had 262 patients below the cut-off 0.16, and 20 of them had PPI. For HbA1c/albumin, HbA1c, albumin, glucose ROC analysis, AUC and *p*-values are given in Table III.

Multivariate Risk Details of Patients With Diabetes Mellitus With Periprosthetic Infection

In the binary logistic regression model and multivariate regression analysis, the rate of HbA1c/albumin was 14.6 times higher than the patients with ≤2.37 cut-off value. (Hba1c/albumin ratio (odds ratio (OR) = 14.6, 95% CI: 3.18-67.1, *p*: 0.01). HbA1c (OR = 2.6, 95% CI: 1.529-4.754, *p*: 0.001), BMI (OR = 1.6, 95% CI: 1.168-2.199, *p*: 0.003), glucose (OR = 1.016, 95% CI: 1.004-1.029, *p*: 0.011), and DM (OR = 0.365, 95% CI: 0.135-0.987, *p*: 0.04) were risk factures for periprosthetic infection. Albumin (OR = 0.503, 95% CI: 0.109-2.314, *p*: 0.378) did not pose a significant risk for periprosthetic infection.

Table II. Comparison of risk factors between groups.

	Group 1	Group 2	*p*-value
HbA1c/albumin	3.13 ± 0.7	2.06 ± 0.6	0.00
Albumin	3.27 ± 0.3 g/dl	4.43 ± 5.3 g/dl	0.502
HbA1c	10.2 ± 2.4%	7.05 ± 1.2%	0.02
Age	60.9 ± 11.5 years	61.4 ± 6.1 years	0.884
BMI	33.6 ± 2.5	30.1 ± 3.04	0.01
Hospital stay	4 ± 2.3 days	4.8 ± 4.2	0.535
Operation time	136.1 ± 2,929 minutes	160.6 ± 33.2 minutes	0.03
ASA	2 ≤ ASA 2/8 > ASA 3	22 ≤ ASA 2/34> ASA 3	0.036

Table III. Diagnostic evaluation of independent predictors of PPI by ROC curve analysis.

Test result variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% confidence interval	
				Lower Bound	Upper Bound
Hba1c/alb ratio	.868	.064	.000	.743	.993
HbA1c	.871	.067	.000	.740	1.000
BMI	.794	.067	.003	.662	.925
Albumin	.614	.077	.252	.463	.766
Glicose	.771	.079	.007	.615	.926

Discussion

The primary finding of this study was found as a prognostic marker in determining the risk of periprosthetic infection after TJA in patients with diabetes mellitus using the HbA1c/albumin ratio. HbA1c/albumin ratio correlated positively with important prognostic markers such as BMI, age, operation time, length of hospital stays, serum glucose, HbA1c, and albumin values.

Infection involving the prosthesis and surrounding tissues is called Periprosthetic infection (PPI)[10]. In the literature, the rate of periprosthetic joint infection varies between 3 and 8%[3,7]. Among the patient groups in these studies, there were healthy individuals. In our study, the PPI rate was 15.15%. This is because only patients with DM were included in the study. It is very important to prevent the occurrence of PPI. For this, preoperative, intraoperative, and postoperative risks should be known. The rate of PPI in diabetic patients has been reported 3-6 times higher than in non-diabetic patients[11]. Jämsen et al[12] demonstrated that glycemic control is effective in preventing infection in the surgical site. In previous studies[12-14], in orthopedic surgery, there was a significant relationship between both preoperative and postoperative glucose levels and PPIs. It has been suggested that hyperglycemia may be a stronger predictor of PPI than diabetes mellitus. However, the number of patients in these studies was low and could not support potential contradictions[15,16]. Glycemic variability may be more valuable than real blood glucose values in predicting PPI risk in joint arthroplasty in TJA[17]. Jämsen et al[12] found a significant relationship with PPI after TKA and THA in patients with HbA1c levels higher than 6.5 mg/dl. Han and Kang[18] showed that the risk of early wound problems is high at HbA1c levels higher than 8 mg/dl, but there is no significant relationship with PPI risk in the long run. In our study, high HbA1c value increased the risk of periprosthetic infection by 2.6. However, our study found that increased HbA1c/albumin ratio after TJA surgery in patients with diabetes mellitus increased the risk of periprosthetic infection by 14.6 times with 90% sensitivity and 62% specificity and was a prognostic marker. In addition, new studies are needed to confirm the correlation between PPI risk and HbA1c/albumin ratio.

Patients with low serum albumin are more likely to develop superficial PPI and develop wound problems. Acute infection, inflammatory disease, kidney disease, liver disease and malnutrition are caused to hypoalbuminemia[19]. Greene et al[20] showed that albumin less than 3.5 g/dl preoperatively increased the risk of PPI 7 times after arthroplasty operations. Huang et al[21] showed in a prospective study of 2,161 patients that low albumin level due to malnutrition was not a risk for PPI. In our study, there was no significant relationship between low albumin levels and PPI. Using the HbA1c/albumin ratio can provide a variable that can combine the information generated by HbA1c and albumin in an index that positively correlates with the infection, i.e., a high rate may indicate high inflammation.

Si et al[22] showed that the risk of PPI infection is increased in patients with a BMI above 30 kg/m2. It has been found that this risk is higher in patients with a BMI>40 kg/m^2. They found that the operation time increased in obese patients, surgical wound and hematoma problems occurred more frequently, and these patients were more immobilized. Claus et al[23] found higher postoperative PPI in patients with a high ASA grade and undergoing total joint arthroplasty. Namba et al[24] showed a significant correlation between PPI rate and increasing ASA value. In our study, we found that in diabetic patients, BMI indices increased the risk of periprosthetic infection by 1.6 fold. In our study, we could not find a significant relationship between ASA score and PPI in diabetic patients.

Limitations

There are some limitations in our study. As in most retrospective studies, the number of patients was low, it is a study of 264 patients due to the problem of finding data. It is also a single-center and small group study that can limit the prognostic value of the HbA1c/albumin ratio. In addition, the rate of infection in our study is higher than in the literature, which may explain why BMI and DM risk results are not compatible with the literature. Finally, additional studies are required for the prognostic marker value of the HbA1c/albumin ratio.

Conclusions

According to our findings, the HbA1c/albumin ratio has a more prognostic capacity than other risks in determining the risk of periprosthetic infection for total joint arthroplasty. HbA1c/albumin ratio is a cheap and easy to apply marker. Patients with an HbA1c/albumin cut-off ratio above 2.37 mg/dl in total joint arthroplasty should be followed more closely for the risk of periprosthetic infection.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study was started prospectively after the approval of the Ethics Evaluation Committee of our faculty (188/04.06.2020).

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Informed Consent

Written informed consent was obtained from all participants.

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